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HOW I DO IT

Lymphatic Mapping and Sentinel Node Biopsy for Early Stage Melanoma: How We Do It at the M. D. Anderson Cancer Center

MERRICK I. ROSS, MD*

Melanoma and Sarcoma Service, Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

INTRODUCTION

The objective of lymphatic mapping is to determine the histologic status of the regional lymph node basin by identifying and obtaining a biopsy of the first draining lymph node(s), the sentinel node(s). This minimally invasive technique promotes a selective approach to lymphadenectomy, allows the application of therapeutic lymph node dissection earlier in the course of disease, and provides valuable staging information. The success of the technique is dependent upon the integration of three components: (1) preoperative determination of regional lymph node basins at risk and predicted number and location of sentinel nodes within the basin (preoperative cutaneous lymphoscintigraphy); (2) intraoperative localization and biopsy of the sentinel node; and (3) careful pathological evaluation of the sentinel node. Candidates for this approach are those Stage I and II melanoma patients predicted to be at intermediate or high risk of harboring occult nodal disease. One of the following primary tumor criteria is used for considering application of this technique: (1) more than 1 mm in thickness; (2) Clark's Level greater than III; (3) the presence of ulceration; or (4) significant regression. The accuracy of the technique is unknown in the patients who have undergone a prior wide local excision of the primary tumor. Since the lymphatic drainage of the remaining skin may be different from that of the original lesion we are therefore in this situation reluctant to offer this option.

PREOPERATIVE LYMPHOSCINTIGRAPHY

The purpose of cutaneous lymphoscintigraphy is threefold: (1) to identify nodal basins at risk in patients who have primary melanomas in anatomic sites where ambiguous drainage is predicted (truncal and head and neck locations); (2) to determine the number and location of sentinel nodes within the basin; and (3) to identify the presence of intransit sentinel lymph nodes located outside the formal lymph node basin. Lymphoscintigraphy is performed with a four-point intradermal injection of approximately 1 millicurie of technetium labeled sulfur colloid or human serum albumin. Following the injection, the material is traced, in real time, to potential nodal basins at risk. When the injection sites are some distance from the nodal basins at risk, the information obtained from the lymphoscintigram is generally straightforward. However, when the injection sites overlie a basin, in at least one plane, clear identification of sentinel node localization may be difficult and at times impossible. Multiple views can be obtained to move the intense radioactivity in the hope of unveiling the location of the sentinel nodes.

Occasionally, the injected colloid will not migrate from the injection site when the lymphoscintigraphy is attempted closely in time following an excisional biopsy. A repeat attempt should be undertaken, waiting approximately a week to ten days to allow the surrounding inflammation to resolve. We generally obtain a formal lymphoscintigram remote from the planned surgery day to allow appropriate surgical planning. However, when the formal lymphoscintigraphy is performed on the morning of the planned surgery, the radioactive material injected for the lymphoscintigraphy can be used for the intraoperative localization with a hand-held gamma probe. It is important to note that if the formal lymphoscintigraphy is performed on the day of the surgery, human serum albumin cannot be used as this agent will

*Correspondence to: Merrick I. Ross, MD, Melanoma and Sarcoma Service, Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.

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migrate very quickly to the sentinel node and then pass on to other secondary echelon nodes. In this situation, the lymphoscintigraphy should always be performed with sulfur colloid.

INTRAOPERATIVE LOCALIZATION AND SENTINEL NODE BIOPSY

We generally use a combination of blue dye and hand-held gamma probe localizations. On the day of surgery, the patient receives a four point intradermal injection of .5 to 1 millicurie of unfiltered technetium labeled sulfur colloid in the Nuclear Medicine Department. This takes place 1 to 4 h prior to initiation of the surgical procedure. A shortened interval may decrease the ability to localize the sentinel node because not enough time will have elapsed to allow passage of the colloid particles to the nodal basin. Significantly longer waiting periods may allow time for the colloid to pass on to secondary echelon nodes leading ultimately to the unnecessary removal of multiple lymph nodes. Using this approach the radioactive ratios of sentinel to non-sentinel nodes approach 100 to 1.

Once entering the operating room, the hand-held gamma probe is used to transcutaneously scan the primary injection site, the intervening soft tissues and the nodal basin proper. Areas of intense radioactivity over the nodal basin are determined and marked with an ''X'' on the skin. The blue dye (Lymphazurin) is then injected circumferentially around the intact primary melanoma or excisional biopsy site. Approximately 3 cc of dye is injected using a tuberculin syringe and a 25 or 27 gauge needle. The patient is then appropriately prepared and draped, allowing adequate time for the dye to travel from the injection site to the nodal basin. Local anesthesia along with intravenous sedation or general anesthesia is usually employed. The type of anesthesia used is more dependent on what is necessary to perform the appropriate wide local excision rather than the sentinel lymph node biopsy. The nodal basin is approached first with a small biopsy incision directed by the hand-held gamma probe. We make sure that this biopsy incision can be easily incorporated into a formal lymphadenectomy incision if that is required. Incision is made over the ''X.'' Once the nodal basin is entered, the localization of the sentinel node is achieved by either following a blue channel towards the blue node or by direct visualization of the lymph node. The visualization of the blue dye is helpful in rapidly identifying which lymph node has accumulated the radioactive colloid. This node is then elevated from the surrounding tissues. Intervening lymphatic channels can be identified because of the blue dye, and are tied to avoid a seroma collection. Ex vivo counts of the node are then achieved with a hand-held gamma probe and recorded in the chart, on a data form, and on the pathology sheet. The lymph node is visually inspected for the presence of macroscopic metastasis or pigment. If the node is clinically normal on macroscopic examination and lacks pigment upon bisecting the lymph node, no frozen sections are performed. After removing the initial node, the nodal basin is then scanned for residual radioactive counts with the hand-held gamma probe. If the background activity in the nodal basin is still high because of the close proximity of the injection site to the nodal basin, we will then proceed with the wide local excision of the primary site. This removes any significant background and allows a more accurate evaluation of residual counts within the nodal basin and intervening tissues. Additional nodes identified by the presence of high radioactivity are then removed and labeled as sentinel nodes, with numbers assigned sequentially in the order of identification.

The sentinel node biopsy cavity is then irrigated, checked for meticulous hemostasis, and closed. In general, no drain is required as little disruption of the lymphatic tissue is performed, particularly when the hand-held gamma probe is utilized.

When the primary injection is remote from the nodal basin, the procedure is relatively straightforward, and what we visualize at the time of surgery using the blue dye should closely mimic the findings of the preoperative lymphoscintigram. However, several situations arise that make the technique somewhat problematic:

1. Close proximity of the injection site to the nodal basin. The amount of radioactive material that remains at the injection site is significantly greater than the amount that travels to the sentinel node. Therefore, when the injection site is close to the nodal basin, the periphery of the injection can mask and/or obscure the ability to localize an area of increased radioactive material within the nodal basin. For example, if the periphery of the injection site has 10,000 counts/second and the sentinel node in the nodal basin only has 8,000 it will be impossible to discriminate the sentinel node from the injection site. If we are unable to localize a sentinel node transcutaneously prior to making an incision, we will make an attempt at visually identifying the sentinel node with the blue dye. If it cannot be identified quickly, we will then excise the primary injection site to remove the high background counts. In this way counts accumulated within the sentinel node can be then unveiled and more easily detected with the hand-held gamma probe.
2. Head and neck locations. Because of the proximity to important structures, the excision margins of primary lesions have to be limited in the head and neck region. We therefore will not inject the blue dye if it cannot be completely removed with the excision of the pri-

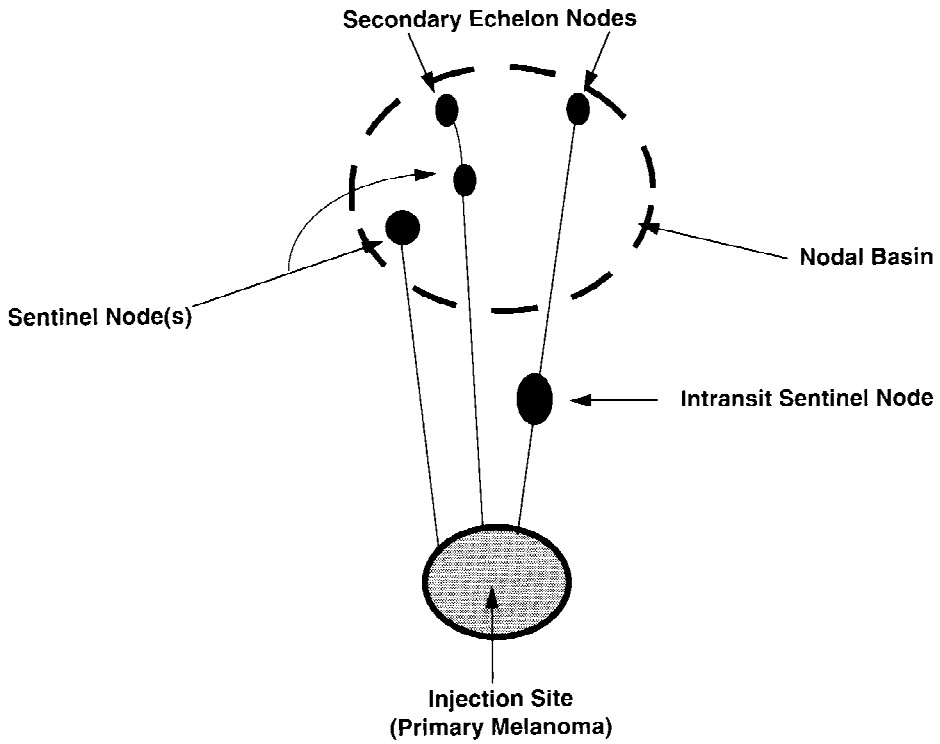

Fig. 1. Schematic presentation of the injection site in relation to the nodal basin and the sentinel nodes.

mary tumor. Residual dye left behind can tattoo the skin for long periods of time. In the head and neck location we will often use colloid injections alone.

3. Identification of intransit sentinel nodes. In specific anatomic locations such as the trunk, 5–10% of the time a lymph node(s) may be identified on preoperative lymphoscintigraphy outside the formal lymph node basin, between the primary injection site and the nodal basin. This lymph node may be the first node of drainage for certain areas of the skin and therefore represents the sentinel node. A similar situation occurs in the extremities either distal to the elbow or to the knee, where the first draining lymph node could either be in the epitrochlear or popliteal regions, respectively. One lymphatic vessel may drain from the injection site to this first intransit node before traveling on, ''in series,'' to the formal nodal basin. However, more than one channel may be identified from an injection site: one traveling to an intransit node and then another channel ''in parallel'' directly to the regional nodal basin. In that situation, both the intransit node and the node within the nodal basin represent sentinel nodes and must both be identified and removed (see Fig. 1). The best way to identify these lymph nodes is: (a) to know that they exist and can be identified on lymphoscintigraphy; and (b) by removing the injection site after identifying a lymph node in the nodal basin and then scanning the intervening tissues with a hand-held gamma probe. Removal of the primary injection site will help detect these intransit nodes.

It is important to remember that the sentinel node is defined as the first node of drainage from a primary injection site or afferent lymphatic channel. However, sometimes the first node that is encountered and visualized by the blue dye may not necessarily be the first node of drainage. The dye and some of the radioactive colloid can travel through the sentinel node into secondary echelon nodes. The first lymph node encountered may actually be a secondary echelon node draining ''in series'' from a deeper or more proximal sentinel node (see Fig. 1). The true sentinel node may be difficult to identify by visual inspection alone. The use of the hand-held gamma probe ensures that the sentinel node is not left behind after removing the initial blue node that was encountered. Significant residual radioactivity will be present in the nodal basin after removal of the secondary echelon node, alerting the surgeon that the actual sentinel node may still be intact.

PATHOLOGIC EVALUATION

The final component of the technique that ensures accurate staging of the nodal basin is careful pathologic evaluation of lymph nodes. Since only one or two lymph nodes are removed, these lymph nodes can be examined

more carefully than routine pathologic assessment. As mentioned above we generally do not perform frozen section evaluation of the sentinel node if this lymph node is clinically negative for metastatic disease. The lymph node is at least serially sectioned for permanent pathologic evaluations and stained with hematoxylin and eosin as well as immunostaining with HMB 45 and S 100 antibodies. The serial sectioning allows a greater sampling of lymph nodes and therefore is more likely to detect the presence of microscopic disease. The immunostaining helps unveil abnormal cells amongst a larger volume of normal lymphocytes. We are presently prospectively evaluating the additional sensitivity of detecting micrometastases by serial sectioning and reverse transcriptase polymerase chain reaction (RT-PCR) for tyrosinase messenger RNA compared to routine histology.

CONCLUSIONS

Successful lymphatic mapping and sentinel node biopsy is not a simple undertaking and requires the sophisticated integration of a multidisciplinary team. The information obtained from this technique is extremely valuable and therefore improper implementation is a disservice to the patient.